

Applicants have amended claims 20 and 23-25 to clarify the subject matter claimed and correct syntax. Applicants have amended claim 30 to correct a typographical error. Applicants have not raised any issues of new matter.

Applicants respectfully request the Examiner to review and enter the above amendments and following remarks into the records. The amendments do not raise any issues that would cause the Examiner to further search and places the application into condition for allowance.

Objection to the Specification

The specifications stands objected to for the use of various trademarks without generic terminology. Applicants respectfully traverse this objection.

The previous response addressed this issue by capitalizing every trademark and indicating terms as being trademarks. The Examiner has acknowledged that the trademarks are properly capitalized, but the Examiner asserts generic terminology is required.

Applicants assert that a skilled artisan would understand trademarked products within the context of the specification. Clearly, a skilled artisan would understand that SUPERDEX 75™ is chromatography material for a gel filtration column. See Page 8, second paragraph. Adding

additional "generic" terminology would only increase the word count and not increase the understanding of the material.

Applicants respectfully request withdrawal of the objection to the specification.

Claim Objection

Claim 30 stands objected to because *Dictyocaulus viviparus* is misspelled. Applicants have corrected the typographical error in claim 30.

Applicants respectfully request withdrawal of the objection to claim 30.

Issue Under 35 U.S.C. §112, First Paragraph

Claim 20 stands rejected under 35 USC 112, first paragraph, as containing subject matter without a sufficient written description. The Examiner asserts that the term "immunogenic part thereof" has no support in the specification and is new matter. Applicants traverse this assertion.

Applicants have amended claim 20 to better reflect what Applicants consider their invention. "The immunogenic protein according to claim 17, comprising the amino acid sequence of SEQ ID NO:30, or an part thereof having

immunogenic properties." The term "immunogenic" fails to constitute new matter, as it is inherent feature of a vaccine component to induce an immune response. Therefore, the only protein or peptides that are functional must have immunogenic properties.

As for support in the specification, Applicants direct the Examiner's attention to page 4, lines 9-10 where Applicants recite "[t]he invention furthermore relates to a protein which comprises the amino acid sequence depicted in Table 6 (SEQ ID NO.: 30) or parts thereof." Also, example 9, on page 11, describes the digestion of Dv17 with a peptidase, resulting in the generation of a number of protein fragments of Dv17. Table 1 on page 14-16 and SEQ ID NOS.: 1-7 list a number of specific fragments of Dv17. Therefore, Applicants have contemplated "parts thereof having immunogenic properties" and more importantly described how to obtain such fragments.

The objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). "The subject matter of the claim need not be described literally . . . in order for the

disclosure to satisfy the description requirement." MPEP §2163.02.

As stated above, Applicants must describe the present invention clearly to allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. Applicants believe they have met such a burden.

Applicants, respectfully, request withdrawal the 35 U.S.C. §112, first paragraph, rejection of claim 20.

Issue Under 35 U.S.C. §112, First Paragraph

Claim 23 stands rejected under 35 U.S.C. §112, first paragraph, as containing subject matter outside the scope of enablement. The Examiner asserts that the specification is not enabling for "parts thereof" of SEQ ID NO:29.

Claim 23 recites an isolated nucleic acid comprising SEQ ID NO:29 or a nucleic acid that hybridizes to SEQ ID NO:29 under stringent conditions. Applicants define the term "stringent conditions" on page 7, in the third paragraph. The defined stringent hybridization conditions of 6 x SSC, 68 °C requires that the fragments be of considerable length and homology to hybridize to the described sequences.

A skilled artisan would not understand the limitations as meaning "a nucleic acid consisting of as few as two

nucleotides", as suggested by the Examiner. Claim 23 as interpreted by the definitions found in the specification, clearly is understandable and enabled. "Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." MPEP §2173.05(b).

A skilled artisan would fully understand how to produce an isolated nucleic acid that hybridizes to SEQ ID NO:29 under stringent conditions, as defined.

Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph rejection.

Issue Under 35 U.S.C. §112, First Paragraph

Claims 24-25 stand rejected under 35 U.S.C. §112, first paragraph as containing subject matter outside the scope of enablement. The Examiner asserts that the specification is not enabling for "parts thereof" of the listed SEQ ID numbers.

Applicants have amended claims 24 and 25 to recite "or parts thereof that hybridize to a sequence of the group under stringent conditions . . .". Applicants have discussed this issue at length in the previous paragraphs. Applicants have clearly contemplated and described the aforementioned "parts thereof." "The test of enablement is

whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Applicants assert that they have met such a burden.

Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph rejection.

Issues Under 35 U.S.C. §112, Second Paragraph

Claims 20 and 23-26 stand rejected under 35 U.S.C. §112, second paragraph, for being indefinite. Applicants traverse this rejection.

The Examiner maintains that the term "parts thereof" is indefinite in claims 20 and 24-25. As explained above, the term "parts thereof" is defined in the specification and examples describe a method to obtain such fragments. "Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." MPEP §2173.05(b). Applicants assert that a skilled artisan would understand the claim language as amended.

Claim 26 stands rejected for being indefinite in the use phrase "expressing the cDNA clone obtained according to

claim 24 . . .". The Examiner bases this rejection on the rejection of claim 24. Applicants have provided sufficient explanation to assert that claim 24 is definite and fully enabled; thus, logic dictates that claim 26 is also definite and fully enabled.

Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

Issue Under 35 U.S.C. §102(b)/103(a)

Claims 17-20 and 29-31 stand rejected under 35 U.S.C. §102(b) for anticipation or, alternatively, under 35 U.S.C. §103(a) for being obvious over de Leeuw et al (Veterinary Parasitology Vol. 39 No. 1-2, 1991, pages 137-147, IDS-10). Claims 17-20 and 29-31 stand rejected under 35 U.S.C. §102(b) for anticipation or, alternatively, under 35 U.S.C. §103(a) for being obvious over Schneider (International Journal of Parasitology, Vol. 22, No. 7, 1992, pages 933-938). Applicants respectfully submit that patentable distinctions exist between the cited prior art and the present invention.

Distinctions Between the Present Invention and de Leeuw et al. and Schneider

Schneider discloses an amino acid sequence of the Dv3-14 protein, which is available as entry AAB27962, from the NCBI protein database. Using standard sequence alignment software, a homology of around 17% is revealed between Dv3-14 and Dv 17, which is SEQ ID No. 30 of the present application. Therefore, a skilled artisan would not find Dv 17 and Dv3-14 related in any manner.

de Leeuw et al. discloses an immunogenic protein of *Dictyocaulus viviparus* with a molecular weight of 17,000 daltons. The Examiner maintains that Applicants' claim limitations reasonably appear to be the identification of new features of a protein already known in the art. The Examiner acknowledged the 37 C.F.R. §1.132 Declaration by Mr. Hoffman, but found the declaration non-persuasive because of lack of factual evidence.

To prove that distinctions actually exist between the cited prior art and the present invention, Applicants submit herewith a Declaration by Dr. Jan Cornelissen, who is a co-author of the publication by de Leeuw.

In the previously submitted Rule 132 declaration, Mr. Hoffman reported that, with respect to de Leeuw et al., he had received a personal communication from Thomas

Schneider, an author of the cited reference, reporting that the 17kd protein disclosed by de Leeuw et al. and the 18kd protein disclosed by Schneider both react with the same monoclonal antibody.

Dr. Cornelissen describes in the attached Rule 132 Declaration an experiment, which proves this assertion. Applicants have attached to the Rule 132 Declaration two copies of gels showing the results of the experiments. From this actual evidence, Dr. Cornelissen concludes that the 17kd protein of de Leeuw et al. and the 18kd protein of Schneider must be similar proteins and, therefore, must be different from the presently claimed proteins because 18kd protein is different from the instant proteins, as stated above.

Therefore, as Dv 17 is not related to Dv 3-14, which is similar to the de Leeuw protein. A skilled artisan definitely would not find the present invention described within the cited references. More, importantly a skilled artisan would not find the present invention obvious from reading the cited references because neither reference provides motivation to alter their teachings in any manner.

Applicants respectfully request withdrawal of the 35 U.S.C. §102(b)/§103(a) rejections over the cited prior art.

Conclusion

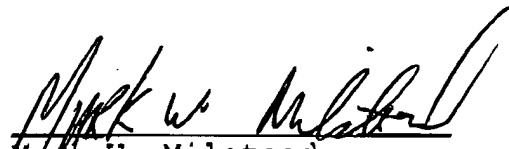
Applicants submit that every issue raised by the outstanding Office Action has been addressed and rebutted. Therefore, the present claims define patentable subject matter and are in condition for allowance.

Attached hereto is a marked-up version of the changes made to the application by this amendment.

Should the Examiner believe that a conference would be helpful in advancing the prosecution of this application, he is invited to telephone Applicants' Attorney at the number below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,



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MWM

Enclosure: Version with Markings to Show Changes Made
37 C.F.R. §1.132 Declaration

Version with Markings to Show Changes Made

IN THE CLAIMS:

The claims have been amended as follows:

20. (Amended) The immunogenic protein according to claim 17, comprising the amino acid sequence of SEQ ID NO:30, or [an immunogenic] part thereof having immunogenic properties.

23. (Twice Amended) An isolated nucleic acid comprising SEQ ID NO:29 or a nucleic acid that hybridizes, under stringent conditions, [with] to a nucleotide sequence according to SEQ ID NO:29.

24. (Twice Amended) A method for identifying a cDNA clone which comprises an isolated nucleic acid sequence according to claim 21, the method comprising:

(b) obtaining a radioactively or nonradioactively labeled oligonucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:8; SEQ ID NO:9; SEQ [I

(b) D] ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; and SEQ ID NO:14, or parts thereof that

hybridize [with] to a sequence of the group under stringent conditions; and

(b) screening a cDNA library prepared from *Dictyocaulus viviparus* using the labeled oligonucleotide molecule.

25. (Amended) A method for identifying a cDNA clone which comprises an isolated nucleic acid sequence according to claim 21, the method comprising:

(a) obtaining a polymerase chain reaction primer having a sequence selected from the group consisting of SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; and SEQ ID NO:14, or parts thereof that hybridize [with] to a sequence of the group under stringent conditions; and

(b) screening a cDNA library or RNAs prepared from *Dictyocaulus viviparus* using the primer.

30. (Amended) A method for immunizing cattle against [*Dictuocaulus*] *Dictyocaulus* *viviparous* comprising administering to a cattle in need thereof a vaccine according to claim 29.

Declaration under 37 CFR § 1.132

Applicant: AKZO Nobel NV
1st Inventor: Hofmann et al.
serial no.: 09/403,092
filed: 15th October 1999
examiner: Zeman, R.A.
group no.: 1645
attorney docketno.: 038311/0103

I, Jan Cornelissen declare as follows,

1. I have the following professional experience. Development of ELISAs for the detection of antibodies directed against parasitic infections in cattle and sheep.
2. I am the co-author of the paper by de Leeuw and Cornelissen (1) that was mentioned by the examiner in his office action of 31st July 2001. In this publication we mention an antigenic 17 kDa protein from *Dictyocaulus viviparus*.
3. I am the author and co-author of the papers by de Cornelissen and de Leeuw (2) and by de Leeuw and Cornelissen (3) in which we describe a monoclonal antibody named CVI-D.viv-500.2.1.1, also referred to as Mab 2. This monoclonal antibody specifically recognizes the 17 kDa D. viviparus antigen described in (1).
4. I have read and understood the paper by Prof. T. Schnieder (4), that was mentioned by the examiner in his office action of 31st July 2001. In this publication is described an 18 kDa protein from D. viviparus adult worms, termed Dv3-14 protein. The cDNA encoding this Dv3-14 was expressed as a GST fusion protein, referred to as DvGST3-14.
5. Two monoclonal antibodies were tested for their ability to recognise D. viviparus antigens; Mab 500.2.1.1 anti D. viviparus and Mab 500.3.1.1 anti D. viviparus both recognise a specific antigen with diagnostic potential from D. viviparus as described by de Leeuw and Cornelissen (1), and which have been characterized by Cornelissen et al. (2), and by de Leeuw and Cornelissen (3). These two anti-D. viviparus monoclonal antibodies Mab 500.2.1.1 and Mab 500.3.1.1, have been evaluated with respect to their reactivity to glutathione S-transferase fusion protein (DvGST3-14) that was blotted to nitro-cellulose from a SDS-PAGE gel. This glutathione S-transferase fusion protein (DvGST3-14) was the product that has been described by Schnieder (4).
6. The antigens blotted were crude adult D. viviparus extract, the DvGST3-14 fusion protein with GST, and the thrombin cut fusion protein Dv3-14 produced according to the methodology as described by de Leeuw and Cornelissen (1) and Schnieder (4).

On each of the two images there is a set of three blots; one set depicts the results of the three blots that were produced from SDS-PAGE gels using non-reducing conditions (marked as: - mercaptoethanol) and the other image

depicts the three blots as produced from gels run under reducing conditions (marked as: + mercaptoethanol), thereby removing possible secondary structures through S-S bridges. Please note that the MWs of the protein bands under non-reducing conditions differ from the MWs under reducing conditions.

In blot I, the 17 Kd antigen of the crude adult worm extract is recognized by *Dictyocaulus* positive bovine serum and by two Mabs anti *D. viviparus* (500.2.1.1. and 5003.1.1.). The mab anti *D. viviparus* 5002.1.1 is the same antibody as was used directly conjugated to HRPO in a *D. viviparus* specific competition ELISA (2).

In blot II, the fusion protein with GST (DvGST3-14) is also recognized by the *D. viviparus* positive bovine serum and by our two mab's anti *D. viviparus*. However, also the 17 kD protein without GST (Dv3-14) is visible, pointing to degradation of the fusion product.

In blot III, the thrombin cut fusion protein (Dv3-14) is detected by neither the bovine serum nor the Mabs. Probably because 100 times less protein of the thrombin cut fusion protein was applied to the gel.

Antibodies used for the incubation:

- A: *Dictyocaulus viviparus* positive bovine serum
- B: *Dictyocaulus viviparus* negative bovine serum
- C: *Fasciola hepatica* positive bovine serum
- D: No bovine serum (negative control)
- E: Mab anti *D. viviparus* 500.2.1.1
- F: Mab anti *D. viviparus* 500.3.1.1
- G: No Mab (negative control)

7. From these recognition patterns in the blots we concluded that the monoclonal antibodies produced against the 17 kDa antigen from *D. viviparus*, do specifically recognise the Major Sperm Protein of *D. viviparus* of Schnieder (4) in the fusion protein with GST (DvGST3-14).
8. Therefore, in my professional opinion the results of the Western blots described above indicate that the 17 kDa antigen described by de Leeuw and Cornelissen in (1) and the Dv3-14 antigen described by Schnieder in (4) are immunologically similar.
9. All statements made herein of my knowledge are true and all statements made on information and belief are believed to be true; these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under section 1001 of Title 18 USC and that such willful false statement may jeopardize the validity of the instant patent application or any patent issuing thereon.

References:

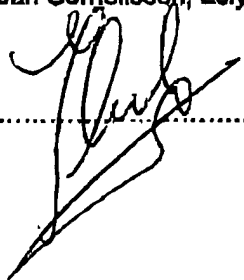
- 1- Leeuw W.A. de, Cornelissen J.B.W.J., 1991. Identification and isolation of a specific antigen with diagnostic potential from *Dictyocaulus viviparus*. Vet. Parasitol. 39: 137-147.
- 2- Cornelissen J.B.W.J, Leeuw W.A. de., 1992. Production and characterization of monoclonal antibodies directed against *Dictyocaulus viviparus* antigens.

Abstr. Vth European Multicolloquium of parasitology, The Hague, page 205, no194.

- 3- Leeuw W.A. d , Cornelissen J.B.W.J., 1993. Comparison of three nzyme immunoassays for the detection of antibodies against *Dictyocaulus viviparus*. Veterinary Parasitology, 49: 229-241.
- 4- Schnieder T., 1992. *Dictyocaulus viviparus*: isolation and characterization of a recombinant antigen with potential for Immunodiagnosis. Int. J. Parasitol. 22(7): 933-8.

Declared by me:

Jan Cornelissen, Lelystad 19 December 2001

A handwritten signature in black ink, appearing to be 'Jan Cornelissen', written over a horizontal dotted line.

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Curriculum Vitae

Name: Cornelissen, J.B.W.J.
First name: Jan
Adres: Edelhertweg 15, ID-Lelystad
Telephone: 0320-238100
Date of birth: 24-12-1959
Place of birth: Nijmegen
Nationality: Dutch nationality
Marital status: Married

Education:

Dutch degrees as technician, comparable with bachelor/master level

from 1977 to 1979 HBO-A, analytical chemistry

from 1979 to 1981 HBO-B, biochemistry

Professional experience

- 1981-1983: Active as biochemical analyst on the department Bio-energetica of the B.C.P. Jansen-Instituut University of Amsterdam.
- 1984-1987: Active as assistant-investigator on the Department of Mammalian Virology en Electron Microscopy Centraal Diergeneeskundig Instituut (Central Veterinary Institute) Lelystad.
- 1987-1990: Active as assistant-investigator on the Department of Parasitology of the Central Veterinary Institute of Lelystad.
- 1990-1998: Active as assistant-investigator on the Department of Immunology of the Central Veterinary Institute, Lelystad
- 1998-1999: Active as senior assistant-investigator on the Department of Immunology Pathology and Epidemiology of the ID-DLO Institute for Animal Health, Lelystad.
- 2000-: Active as senior assistant-investigator on the Division Animal Sciences of the ID-Lelystad Institute of Animal Health, Lelystad.

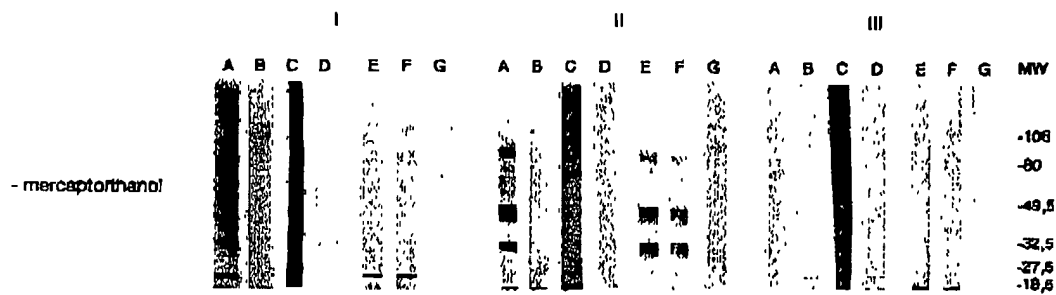
Publications last five years as first author.

- 1- Cornelissen J.B.W.J., Milligen van F.J., Borgsteede F.H.M. (1996). Validation of an ELISA for the diagnosis of *Dictyocaulus viviparus* infections in cattle by interlaboratory tests. *Parassitologia* 38, EMOP VII abstracts Dg13 p282.
- 2- Cornelissen J.B.W.J., Borgsteede F.H.M., van Milligen F.J. Evaluation of an ELISA for the routine diagnosis of *Dictyocaulus viviparus* infections in cattle (1997). *Veterinary Parasitology* 70: 153-164.
- 3- Jan B.W.J. Cornelissen¹, Cor P.H. Gaasenbeek, Fred Borgsteede, Wim Boersma and Florine J. van Milligen (1999). Pre-selected epitope of cathepsin-L₁ in a peptide based immunoassay for the diagnosis of *Fasciola hepatica* infections in cattle. *International Journal for Parasitology* 29:685-696.
- 4- Jan B.W.J. Cornelissen¹, Cor P.H. Gaasenbeek, Wim Boersma, Fred Borgsteede and Florine J. van Milligen (1999). Pre-selected epitope of cathepsin-L₁ in a peptide based immunoassay for the diagnosis of *Fasciola hepatica* infections in cattle. Poster: World Veterinary congress WVA 23-26 september 1999, Lyon, France.
- 5- Jan B.W.J. Cornelissen, Cor P.H. Gaasenbeek, Fred H.M. Borgsteede, Wicher G. Holland, Michiel M. Harmsen and Wim J.A. Boersma. Early immunodiagnosis of fasciolosis in ruminants using recombinant *Fasciola hepatica* cathepsin L-like protease. *International Journal for Parasitology*. 2001: Vol 31/7, pp 728-737.

I Dictyocaulus viviparus
crude adult worm extract

II 3-14 p GEX-2T
Fusionprotein mit GST (Dv GST 3-14)

III 3-14 p GEX-2T (Dv 3-14)
Fusionprotein, Thrombin geschnitten



TOTAL P.28 ~
+ mercaptoethanol

